REMARKS

I. In Item 2 of the Office Action, claims 1-3, 8, 27, 28, 30, 31, 43 and 45-47 were rejected under 35 USC 102(b) over WO99/26480.

The rejection is traversed for the following reasons.

As stated in the record and incorporated by reference herein, a reference that does not enable and place a teaching in the public domain cannot and does not anticipate, see, for example, *Paperless Accounting, Inc. v. Bay Area Rapid Transit Sys.*, 804 F.2d 659, 231 USPQ 649 (Fed. Cir. 1986) cert denied, 480 U.S. 933 (1987), of record, and *Rockwell International Corp. v. United States*, 147 F.3d 1358, 47 USPQ 2d 1027 (Fed. Cir. 1998), of record.

WO99/264890 ("the PCT") purports to use gene therapy to treat aberrant angiogenesis, primarily the vascularization associated with cancer.

As argued herein and in the record, WO99/26480 is not enabled for ocular gene therapy with endostatin. WO99/26480, as a whole, teaches, at best, expression of angiostatin with a goal of treating cancer. WO99/26480 does not describe how to obtain ocular gene therapy with endostatin. The document makes mere passing mention of a number of methods, reagents and targets without any enabling teaching thereof.

Attached hereto is a second sworn Declaration teaching the state of the art of endostatin at the time the application was filed. The attached Declaration of Dr. Guo of the University of Southern Mississippi stated that, for example, in 1998, it was clear much of the original research on endostatin of the Folkman laboratory could not be repeated, programs attempting to find a biological activity for endostatin were terminated and clinical trials were unsuccessful, see the copy of King attached to the Guo Declaration. For example, NCI scientists were unable to demonstrate an antiangiogenic activity, page 1, fourth full paragraph of King. In that same paragraph, King reported that Genentech tried to duplicate the Folkman research over a period of a year without success and terminated their program. EntreMed, the Maryland company that licensed to commercialize endostatin, could not duplicate the Folkman results, page 1, fifth full paragraph of King.

Jouanneau et al. (copy attached to the Declaration of Guo, and discussed in paragraph 9 thereof) reported a lack of antitumor activity of endostatin in a tumor model. (One of the co-authors of Jouanneau et al. is Philippe Leboulch, the named first inventor of WO99/26480). In Jouanneau et al., the SKNAS tumor cell line was injected into nude mice expressing endostatin, similar to the method taught in Example 5 of WO99/26480. Although serum endostatin levels were high, no alteration in tumor growth was noted.

In another publication discussed in and attached to the Guo Declaration, Dr. Leboulch was quoted in Mandavilli, "We could not see an effect of endostatin any way we tried."

The reports of Leboulch not being able to demonstrate an antiangiogenic activity of endostatin in cancer evidence his inability to replicate the results of Dr. Folkman or to prove the teachings of his PCT application. In conjunction with other negative reports of an in vivo effect of endostatin in cancer, the artisan would conclude that there is a lack of operability of endostatin.

That very scenario was determinative in *Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp. and Schering Corp.*, 320 F.3d 1339, 65 USPQ2d 1961 (Fed. Cir. 2003). The *Boehringer* case involved effective publications reporting failure to replicate the teachings of the Boehringer patent. Two references described unsuccessful attempts to isolate the PRRS virus, which was isolated and claimed in the Boehringer patent. Those negative reports of the independent inability to practice the teachings of the Boehringer patent were directly relevant in disabling the attempt by Schering to invalidate the Boehringer patent.

Hence the inability of artisans to replicate teachings goes to the operability and enablement of those teachings, which, for the instant application, relate to a publication and not to a patent.

For the reasons above and of record, WO99/26480 does not satisfy the written description and enablement requirements of a reference as to treating ocular diseases with endostatin. The teaching therein is insufficient and, as shown in the literature, not reproducible. The PCT does not place the claimed invention into the hands of the public. Thus, WO 99/26480 is not an effective reference as to the invention of interest. Hence, there is no anticipation. Accordingly, withdrawal of the rejection is requested respectfully.

II. On page 4-10 of the Office Action, claims 1 and 29; claims 1 and 32; claims 1, 33 and 38; and claims 1, 33, 38-41 and 48-50 were rejected under 35 USC §103(a) over, in each rejection, WO99/26480, in view of Keshet et al. and Otani et al.; the '826 patent; the '107 patent; and the '107 patent and the '826 patent, respectively. The Examiner detailed a number of deficiencies in WO99/26480 in constructing the rejection.

The rejections are traversed for the following reasons.

As discussed hereinabove and in the record, and herein incorporated by reference, WO99/26480 is not enabled as to the instant application and is legally insufficient to teach ocular gene therapy with endostatin, and particularly the claimed method of administering the particular vectors of interest directly to the eye.

Seeking guidance, once again, from the *Boehringer* case, copy attached hereto for the convenience of the Examiner, there, two references described failed attempts to duplicate the teachings of the patent in suit. Although other effective references were of record, the Federal Circuit noted that a showing of obviousness requires a motivation or suggestion to combine or to modify prior art references, coupled with a reasonable expectation of success. The Federal Circuit stated, "...there can be little better evidence negating an expectation of success than actual reports of failure." page 1354.

Attached hereto is the Declaration of Guo. In the Declaration, Dr. Guo confirmed the knowledge of negative results of any alleged in vivo endostatin activity in cancer. Dr. Guo discussed a brief paragraph appearing in Science magazine; and the publication of Bachelot et al., yet another article co-authored by Leboulch reporting no in vivo antiangiogenesis activity in cancer for endostatin. Endostatin research was not reproducible, not consistent and not practicable. Dr. Guo referred to several publications and reports attesting to the state of endostatin research, namely the lack of reproducibility of the original Folkman research and the growing skepticism that endostatin had any antiangiogenesis activity in cancer, using a variety of models. Dr. Guo observed that endostatin experiments relating to delivery of the endostatin gene as compared to delivery of endostatin protein yielded more fluctuating and disappointing results.

On page 11 of the Office Action, the Examiner stated, "It is not required that Leboulch et al. provide an enabling disclosure for using endostatin gene therapy to treat cancer."

However, the issue of the inability of endostatin to curtail cancer growth is probative. The first and only in vivo use of endostatin was directed to attempts to treat cancer. As found by a number of research groups, endostatin was inoperative in having an effect on cancer. Thus, the first indication was inoperable. That the first tested indication is inoperable is probative on the use of endostatin per se. Clearly, there is no reasonable expectation whether endostatin would have any biological activity because of the failure with cancer. Moreover, the PCT provides a passing mention of numerous embodiments, does not provide an enabled teaching on the in vivo use of endostatin, and is but a mere publication, one that was not peer-reviewed, and which has been abandoned by the applicant.

The Examiner cited U.S. Patent Nos. 5,854,205 and 6,174,861 as support the conclusion that endostatin is an anti-angiogenic factor. The '205 and '861 patents have the same disclosure.

Those two patents are those of Dr. Folkman, the source of the very research which has not stood up to scientific scrutiny and the foundational aspect of science, reproducibility. Some of the references of record report the failed attempts of investigators at the same institution as that of Dr. Folkman to duplicate the original observations of Dr. Folkman as well as the teachings of WO99/26480.

As stated on the record and known in the art, EntreMed licensed the technology of Dr. Folkman, see the attached copy of the EntreMed license listing on the last page in Appendix A, U.S. Ser. No. 60/005,835, a benefit case of the '861 and '205 patents, and which also lists applications in the family by the 2 August 1996 and 22 October 1996 filing dates of another provisional and a non-provisional applications, respectively, that relate to the '861 and '205 patents. EntreMed was the vehicle for the attempted commercialization of the Folkman technology. EntreMed has since abandoned those efforts.

The Examiner cited U.S. Patent No. 6,201,104 to EntreMed.

The '104 patent relates to a receptor, not to an angiogenesis factor.

The Examiner questioned the objectivity of the sworn Declaration of Dr. Connelly. For example, the Examiner questioned how Dr. Connelly knew many of the Examples were not actually conducted.

The sworn Declaration of Dr. Connelly arose from a discussion with the undersigned and is based on her own recollections as a scientist intimate with the biotech community which involves EntreMed and Genetix, the company of Dr. Leboulch.

Nevertheless, as the sworn Connelly Declaration relates to the state of the art of endostatin at the time of the invention, attached hereto is a second sworn Declaration confirming those facts. In his Declaration, Dr. Guo summarized the published reports on the inoperability of endostatin, which led to the conclusion that administered endostatin had no biological effect in the treatment of cancer. Dr. Guo also summarized the state of the art as to the diversity of angiogenesis in different tissues. Thus, angiogenesis in cancer is distinct from angiogenesis in the non-cancerous eye.

Accordingly, the evidence of record, including the post-filing evidence reporting independent failures to replicate the teachings of WO99/26480, U.S. Patent No. 5,827,702 and U.S. Patent No. 6,206,104, clearly and convincingly demonstrate that the above three documents are not enabled. "In order to render a claimed apparatus or method obvious, the prior art must enable one skilled in the art to make and use the apparatus or method." *Beckman Instructions, Inc. v. LKB Produkter AB*, 892 F.2d 1547, 1551, 13 USPQ 2d 1301, 1304 (Fed. Cir. 1989), of record.

There are no working examples demonstrating the successful expression and use of endostatin to treat any model of angiogenesis in the PCT. Because no experimentation to make and to use endostatin to treat ocular diseases is provided in WO99/26480, and in light of the state of the art demonstrating no reproducibility of the endostatin research in cancer, an undue amount of experimentation is needed to practice the teachings of WO99/26480 for reducing angiogenesis in ocular diseases with a reasonable expectation of success.

Although the only attempted in vivo use of endostatin was to treat cancer, which ended in failure, the Examiner took the position that evidence does not detract from the in vivo use of endostatin for other indications, in the absence of any such evidence.

Applicants are unaware of any evidence that endostatin had been shown to have any in vivo efficacy in any non-cancer tissues when the instant application was filed, and there is no such evidence of record.

Instead, Applicants have provided clear and convincing evidence that at the time the application was filed, use of endostatin was not enabled. There was no evidence endostatin had an in vivo effect because the first and only attempt at observing a biological effect of endostatin, which was an attempt in halting tumor growth, was unsuccessful. Thus, there was no reasonable expectation that endostatin would have any useful activity in vivo, and certainly no reasonable expectation that endostatin could treat non-cancer ocular diseases characterized by inappropriate and dysfunctional neovascularization. Accordingly, prima facie cases of obviousness have not been made and the rejections can be removed.

CONCLUSION

Applicants submit that the pending claims are in condition for allowance and early indication of such is requested respectfully. Reexamination, reconsideration, withdrawal of the rejections and early passage of the application to issuance are solicited earnestly. If any fees are found to be applicable, please charge any additional fees or make any credits to Deposit Account No. 02-1818.

Respectfully submitted,

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BY _____

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